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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,917	02/10/2004	Bo Hansen	58609 (71432)	2108

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/776,917	HANSEN ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-11,13-18,47-54,64-76 and 78-90* is/are pending in the application.

4a) Of the above claim(s) *64-76, and 78-90* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-11,13-18 and 47-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date ~~7/14/04~~ 8/29/05, 12/6/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received on 3/21/06.

Claims 5, 12, 17-46, 55-63, and 77 are canceled.

Applicant's election of group 1 and SEQ ID NO:30 is acknowledged. Claims 64-76, and 78-90 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/21/06.

Claims 1-4, 6-11, 13-18, 47-54, 64-76, and 78-90 remain pending.

Claims 1-4, 6-11, 13-18 and 47-54 are under consideration in this Office Action.

Claim Objections

Claim 10 is objected to because "nucleobases" should be singular, not plural.

Claim 13 is objected to because it refers to a Figure. Applicant is referred to MPEP 2173.05(s) which states:

> Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." Ex parte Fressola, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted). Reference characters corresponding to elements recited in the detailed description and the drawings may be used in conjunction with the recitation of the same element or group of elements in the claims. See MPEP § 608.01(m).

Appropriate correction is required.

Claim 50 is objected to because "calmette-gurin" is misspelled in line 5, "etopside" is misspelled in line 11, and "tamoxifin" is misspelled in line 19.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10 and 13-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is indefinite to the extent that it depends from cancelled claim 5.

Claims 13 and 15 are indefinite because they recite "the antisense" without antecedent basis.

Claim 14 is indefinite to the extent that it depends from cancelled claim 12.

Regarding claim 50, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 102

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 15, 47-52 and 54 are rejected under 35 U.S.C. 102(e) as being anticipated by McSwiggen (US 20030153521).

McSwiggen taught antisense oligonucleotides targeted to a variety of sequences in H-Ras. See e.g. paragraph 10. The antisense molecules are DNA, include

nucleotide analogues, and are between about 15 and 75 nucleotides in length. See paragraphs 82 (at page 8), 106, 107, and 140-142. Targets for antisense oligonucleotides include those listed in Table III, including SEQ ID NO: 3061. See paragraph 91 and page 74. SEQ ID NO: 3061 is 5'GGAGUACAGCGCCAUGC3'. It follows that antisense DNA targeting SEQ ID NO:3061 comprises the base sequence 5'GCATGGCGCTGTACTC3', which is bases 1-16 of instant SEQ ID NO:30. McSwiggen taught conjugates comprising the antisense compound at paragraphs 144, 185, and 191. Pharmaceutical compositions and salts are disclosed throughout the specification, e.g. at paragraphs 45, 188, 191, and 193. The antisense molecules are also conjugated to biologically active molecules such as chemotherapeutic agents (e.g. paclitaxel (Taxol), docetaxel, cisplatin, methotrexate, doxorubicin, fluorouracil carboplatin, gemcitabine, and vinorelbine). See paragraphs 144-147 and 231.

Thus McSwiggen anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 6, 7-9, 11, 13-16, 47-52, and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over McSwiggen (US 20030153521) in view of Wahlestedt et al (Proc. Nat. Acad. Sci. USA 97(10): 5633-5638, 2000).

McSwiggen taught antisense oligonucleotides targeted to a variety of sequences in H-Ras. See e.g. paragraph 10. The antisense molecules are DNA, include nucleotide analogues, and are between about 15 and 75 nucleotides in length. See paragraphs 82 (at page 8), 106, 107, and 140-142. Targets for antisense oligonucleotides include those listed in Table III, including SEQ ID NO: 3061. See paragraph 91 and page 74. SEQ ID NO: 3061 is 5'GGAGUACAGCGCCAUGC3'. It follows that antisense DNA targeting SEQ ID NO:3061 comprises the base sequence 5'GCATGGCGCTGTACTC3', which is bases 1-16 of instant SEQ ID NO:30. McSwiggen taught conjugates comprising the antisense compound at paragraphs 144, 185, and 191. Pharmaceutical compositions and salts are disclosed throughout the specification, e.g. at paragraphs 45, 188, 191, and 193. The antisense molecules are also conjugated to biologically active molecules such as chemotherapeutic agents (e.g. paclitaxel (Taxol), docetaxel, cisplatin, methotrexate, doxorubicin, fluorouracil carboplatin, gemcitabine, and vinorelbine). See paragraphs 144-147 and 231. Other chemotherapeutic agents are considered obvious variants.

McSwiggen did not teach locked nucleic acids (LNAs).

Wahlestedt taught gapmer antisense oligonucleotides comprising beta-D-oxy locked nucleic acids, and demonstrated that these had superior stability to exonucleases, formed more stable complexes with target mRNAs than did conventional antisense oligonucleotides, and stimulated RNase H. See e.g. abstract, Table 1 on page 5634, Fig. 3 on page 5636, Fig. 4 on page 5637, Fig. 6 on page 5638. Nine of the fifteen nucleotides were LNAs.

It would have been obvious to one of ordinary skill in the art at the time of the invention to make the antisense oligonucleotides of McSwiggen using the LNAs and gapmer organization of Wahlestedt. One would have been motivated to do so in order to obtain the performance characteristics taught by Wahlestedt, e.g. high binding affinity, thermostability, and RNase H activation.

Thus the invention as a whole was prima facie obvious.

Claims 1-4, 6-11, 15, 16, 47-52, and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over McSwiggen (US 20030153521) in view of Wengel et al (US 6,670,461).

McSwiggen taught antisense oligonucleotides targeted to a variety of sequences in H-Ras. See e.g. paragraph 10. The antisense molecules are DNA, include nucleotide analogues, and are between about 15 and 75 nucleotides in length. See paragraphs 82 (at page 8), 106, 107, and 140-142. Targets for antisense oligonucleotides include those listed in Table III, including SEQ ID NO: 3061. See paragraph 91 and page 74. SEQ ID NO: 3061 is 5'GGAGUACAGCGCCAUGC3'. It follows that antisense DNA targeting SEQ ID NO:3061 comprises the base sequence 5'GCATGGCGCTGTACTC3', which is bases 1-16 of instant SEQ ID NO:30. McSwiggen taught conjugates comprising the antisense compound at paragraphs 144, 185, and 191. Pharmaceutical compositions and salts are disclosed thought the specification, e.g. at paragraphs 45, 188, 191, and 193. The antisense molecules are also conjugated to biologically active molecules such as chemotherapeutic agents (e.g.

paclitaxel (Taxol), docetaxel, cisplatin, methotrexate, doxorubicin, fluorouracil carboplatin, gemcitabine, and vinorelbine). See paragraphs 144-147 and 231. Other chemotherapeutic agents are considered obvious variants.

McSwiggen did not teach locked nucleic acids (LNAs).

Wengel taught that LNA nucleotides gave higher thermostability than normal nucleic acids, and that the use of high affinity LNA monomers should facilitate the construction of antisense probes of sufficient thermostability to hybridise effectively to such target RNAs. provide a wide range of improvements for oligonucleotides used in diagnostics and therapy. See abstract, column 40, lines 40-48, and Figs. 2 and 25-41.

Regarding instant claims 7 and 11, Wengel disclosed oxy-LNAs, amino-LNAs, thio-LNAs, and a variety of other structures for claimed variables X and Z. See column 11, lines 3-32. A variety of D-beta nucleosides is disclosed (see e.g. Examples 92-104 at columns 83-87), although all stereoisomers are contemplated (see column 19, line 32 to column 20, line 13.

Internucleoside linkages of instant claim 9 are disclosed at column 20, line 62 to column 21, line 51 of Wengel, especially at column 21, lines 30-44. Modified bases taught by Wengel include diaminopurine, 5-methylcytosine, 5-bromouracil, isocytosine, pseudoisocytosine, and inosine. See column 1, lines 47-63. Any routinely-used base is considered to be an obvious variant.

In one embodiment, the fraction of LNAs in a given oligonucleotide ranges from 0.01% to 100%. See column 20, lines 16-25 and column 22, lines 20-43.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the locked nucleic acids of Wengel as modified oligonucleotides in the antisense molecule of McSwiggen. One would have been motivated to do so in order to obtain the performance characteristics taught by Wengel, e.g. high binding affinity and thermostability.

Thus the invention as a whole was prima facie obvious.

Claim 53 is rejected under 35 U.S.C. 103(a) as being unpatentable over McSwiggen (US 20030153521) and Wahlestedt et al (Proc. Nat. Acad. Sci. USA 97(10): 5633-5638, 2000) as applied to claims 1, 2, 4, 6, 7-9, 11, 13-16, 47-52, and 54 above, and further in view of Crooke (Antisense Research and Application, Springer-Verlag, Berlin, Germany, vol. 131, pp. 103-140, 1998).

The teachings of McSwiggen and Wahlestedt are summarized above and can be combined to render obvious a pharmaceutical composition comprising antisense oligonucleotides of 12-50 bases comprising 16 nucleotides of instant SEQ ID NO:30 and oxy beta-D locked nucleic acids.

These references do not teach an antisense oligonucleotide as a prodrug.

Crook taught that delivery of antisense oligonucleotides to cells can be facilitated by preparing the oligonucleotides in a protected manner so that the oligo is neutral when it is administered. Protection groups are designed in such a way that so they can be removed then the oligo is taken up by the cells. Examples of such protection groups are S-acetylthioethyl (SATE) or S-pivaloylthioethyl (t-butyl-SATE). These protection

groups are nuclease resistant and are selectively removed intracellularly. See the instant specification at paragraph bridging pages 28 and 29.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the protected nucleic acids of Crook in the invention of McSwiggen as modified by Wahlestedt. One would have been motivated to do so in order to facilitate cellular uptake of the antisense oligonucleotides.

Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635